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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,838	07/13/2001	Avi Ashkenazi	10466/72	5331

35489 7590 09/09/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,838	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The preliminary amendment(s) filed August 26, 2002 and July 13, 2001 have been entered. Claims 39-51 are pending and being examined.

Priority

The present claims are directed to or encompass a polypeptide comprising the amino acid sequence of SEQ ID NO: 114. Based on the priority statement filed August 26, 2002 and an inspection of the patent applications, the examiner has concluded that the claimed subject matter is supported by the disclosure in application serial no. PCT/US00/04414, filed February 22, 2000 but is not supported by any of the others because the claimed subject matter is not supported in the manner provided by 35 U.S.C. 112, first paragraph in any of the earlier filed applications. Also, the limitation "extracellular domain" is new matter with respect to any of the other applications filed prior to February 22, 2000. Also, prior to February 22, 2000 the PRO317 polypeptide is not supported by either a specific and substantial asserted utility or a well established utility, and one skilled in the art clearly would not know how to use the claimed invention. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. Accordingly, the claimed subject matter has an effective filing date of February 22, 2000.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to February 22, 2000 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims

which applicant considers to have been in possession of and fully enabled for prior to February 22, 2000.

The following rejections under 35 U.S.C. §§ 102 and 103 are made under the assumption that the effective filing date for the instantly claimed invention is February 22, 2000.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See, for example, page 167, line 38. This is not meant to be an exhaustive list of places where the specification contains an embedded hyperlink and/or other form of browser-executable code. Applicant's cooperation is requested in deleting all embedded hyperlinks and/or other forms of browser-executable code.

Appropriate correction is required.

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See page 14, line 17. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested

in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

Information Disclosure Statement

The sequences in the information disclosure statement filed March 14, 2002 (Paper No. 10) have been considered to the extent possible, but a residue by residue comparison has not been done. The "Other Art" will not be listed on any patent resulting from this application because it was not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 or PTO/SB/08A and 08B form, must be filed within the set period for reply to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-43, 50, 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 114 wherein said polypeptide induces the proliferation of chondrocytes, does not reasonably provide enablement for such a polypeptide not identical to SEQ ID NO: 114 that does not have this activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 114 or to some portion thereof. There is no functional limitation in the claims. Applicants have taught a polypeptide comprising the amino acid sequence of SEQ ID NO: 114 and the secreted form thereof, lacking its associated signal sequence. This polypeptide was shown to induce the proliferation of chondrocytes in an in vitro assay (example 99 at pages 236-237).

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. While the specification suggests that the PRO317 polypeptide is a TGF-β superfamily member, what TGF-β superfamily-related function it possesses aside from stimulating chondrocyte proliferation is undisclosed. As opposed to the claims, what is disclosed about PRO317 is narrow: a single polypeptide with one disclosed function and no other obvious specific functions. Knowledge of one TGF-β related polypeptide's structure and function does not provide predictability about the function of a genus of polypeptide's having at least 80% amino acid sequence identity thereto. For example, Vukicevic (A, PTO-892 2003-09-07) teaches that OP-1 promotes cell condensations and tubulogenesis in metanephric mesenchyme but BMP-2, a closely related member of the TGF-β-superfamily, and TGF-β1 had no effect (page 9023, paragraph bridging columns 1-2). Vukicevic establishes that closely related members of the TGF-β superfamily have unpredictable effects.

There are no working examples of polypeptides having an amino acid sequence less than 100% identical to the amino acid sequence of SEQ ID NO: 114 or to some portion thereof. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the chondrocyte proliferative function disclosed in the instant specification. While the specification generally describes properties of TGF-β superfamily members, it is acknowledged that functional properties of TGF-β superfamily members are diverse (pages 15-17). The specification does not provide guidance for using polypeptides related to (i.e., 80%-99% identity) but not identical to the amino acid sequence of SEQ ID NO: 144, which do not have the single specific disclosed activity show for PRO317.

The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of TGF-β superfamily members and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO: 114, the one limited working example of PRO317 polypeptide and its one function, the lack of direction or guidance for using polypeptides that are not identical to at the amino acid sequence of SEQ ID NO: 114, lacking the associated signal peptide, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claims 39-43, 50, 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 114, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 39-44, 47, 48, 50, 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The PRO317 polypeptide, and the TGF-β superfamily of polypeptides to which it belongs, are soluble proteins, and are not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain ... lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39-43, 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Celeste (A, 2003-09-07PTO-892 2003-09-072003-09-07). Celeste discloses an isolated human BMP-17 polypeptide (column 2, full paragraph 1) having an amino acid sequence that is 99.6% identical to the amino acid sequence of SEQ ID NO: 114 and 99.6% identical to the amino acid sequence of amino acids 19-366 of SEQ ID NO: 114 of the present application, as indicated below:

```
RESULT 1
; Patent No. 6027917
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  366 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein

  Query Match             99.6%;  Score 1920;  DB 3;  Length 366;
  Best Local Similarity   99.7%;  Pred. No. 3.8e-199;
  Matches  365;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy       1 MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ 60

Qy      61 YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL 120

Qy     121 FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180

Qy     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240

Qy     241 DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP 300
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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```
Db    241 DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP 300

Qy    301 PEALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360
          ||||||||||||||||||||| ||||||||||||||||||||||||||||||||||||||
Db    301 PEALAFKWPFLGPRQCIASETASLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360

Qy    361 PRRLQP 366
          ||||||
Db    361 PRRLQP 366
```

```
RESULT 1
; Patent No. 6027917
;  GENERAL INFORMATION:
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  366 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein

  Query Match             99.6%;  Score 1811;  DB 3;  Length 366;
  Best Local Similarity   99.7%;  Pred. No. 1.3e-192;
  Matches  347;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy      1 GAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYVALLQRSHGDRSRGKRF 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     19 GAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYVALLQRSHGDRSRGKRF 78

Qy     61 SQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPKAALHRHGRLSP 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     79 SQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPKAALHRHGRLSP 138

Qy    121 RSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVNFWQQLSRPRQPLL 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    139 RSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVNFWQQLSRPRQPLL 198

Qy    181 LQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTLDLGDYGAQGDCDPEAPMT 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    199 LQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTLDLGDYGAQGDCDPEAPMT 258

Qy    241 EGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPPEALAFKWPFLGPRQCIA 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    259 EGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPPEALAFKWPFLGPRQCIA 318

Qy    301 SETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 348
          ||| ||||||||||||||||||||||||||||||||||||||||||||
Db    319 SETASLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 366
```

Celeste also discloses a chimeric polypeptide comprising a human BMP-17 polypeptide and a heterologous polypeptide (column 10, full paragraph 3).

Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Meno (V,2003-09-07 PTO-892 2003-09-072003-09-07). Meno discloses an isolated polypeptide (Figure 2) having an amino acid sequence that is 82.7% identical to the

amino acid sequence of SEQ ID NO: 114 and 84.2% identical to the amino acid sequence of amino acids 19-366 of SEQ ID NO: 114 of the present application, as indicated below:

```
S67507
morphogen lefty precursor - mouse
C;Species: Mus musculus (house mouse)
C;Date: 19-Mar-1997 #sequence_revision 18-Jul-1997 #text_change 05-Nov-1999
C;Accession: S67507
R;Meno, C.; Saijoh, Y.; Fujii, H.; Ikeda, M.; Yokoyama, T.; Yokoyama, M.; Toyoda, Y.; Hamada, H.
Nature 381, 151-155, 1996
A;Title: Left-right asymmetric expression of the TGF-beta-family member lefty in mouse embryos.
A;Reference number: S67507; MUID:96202359; PMID:8610011
A;Accession: S67507
A;Molecule type: mRNA
A;Residues: 1-368 <MEN>
A;Cross-references: EMBL:D83921; NID:g1325920; PIDN:BAA12121.1; PID:d1012795; PID:g1435051
A;Note: the authors translated the codon ACG for residue 241 as His
C;Keywords: growth factor
F;78-368/Product: morphogen lefty #status predicted <MAT1>
F;136-368/Product: morphogen lefty #status predicted <MAT2>

  Query Match            82.7%;  Score 1594;  DB 2;  Length 368;
  Best Local Similarity  81.9%;  Pred. No. 1.3e-123;
  Matches  299;  Conservative   24;  Mismatches   40;  Indels    2;  Gaps    1;

Qy      4 LWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYVA 63
          ||||||||  | | |   ||||||:|||||:|||| : | ||:||:| :|||:||| ||||
Db      4 LWLCWALWALSLVSLREALTGEQILGSLLQQLQLDQPPVLDKADVEGMVIPSHVRTQYVA 63

Qy     64 LLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRLFQE 123
          ||| ||  |||||||||: ||||||||  | ||||||||||||||||||||||||||||||
Db     64 LLQHSHASRSRGKRFSQNLREVAGRFLVSETSTHLLVFGMEQRLPPNSELVQAVLRLFQE 123

Qy    124 PVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEA 183
          |||: || |  |||| |||||||:|||| ||||||||:|||||||:||||||||||||
Db    124 PVPRTALRRQKRLSPHSARARVTIEWLRFRDDGSNRTALIDSRLVSIHESGWKAFDVTEA 183

Qy    184 VNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAP--AGLGEPQLELHTLD 241
          ||||||||||||||||||||||||||||     :|||||||:|| |   | ||||||||||
Db    184 VNFWQQLSRPRQPLLLQVSVQREHLGPGTWSSHKLVRFAAQGTPDGKGQGEPQLELHTLD 243

Qy    242 LGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPP 301
          | ||||||:||||||:||||||||||||:||||||||||:||||||| |||||:| | |
Db    244 LKDYGAQGNCDPEAPVTEGTRCCRQEMYLDLQGMKWAENWILEPPGFLTYECVGSCLQLP 303

Qy    302 EALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVP 361
          |:|  :||||||||:|||  |||||||:|||||||||||||||| |||||||||:|
Db    304 ESLTSRWPFLGPRQCVASEMTSLPMIVSVKEGGRTRPQVVSLPNMRVQTCSCASDGALIP 363

Qy    362 RRLQP 366
          |||||
Db    364 RRLQP 368


S67507
morphogen lefty precursor - mouse
C;Species: Mus musculus (house mouse)
C;Date: 19-Mar-1997 #sequence_revision 18-Jul-1997 #text_change 05-Nov-1999
C;Accession: S67507
R;Meno, C.; Saijoh, Y.; Fujii, H.; Ikeda, M.; Yokoyama, T.; Yokoyama, M.; Toyoda, Y.; Hamada, H.
Nature 381, 151-155, 1996
A;Title: Left-right asymmetric expression of the TGF-beta-family member lefty in mouse embryos.
A;Reference number: S67507; MUID:96202359; PMID:8610011
A;Accession: S67507
A;Molecule type: mRNA
A;Residues: 1-368 <MEN>
A;Cross-references: EMBL:D83921; NID:g1325920; PIDN:BAA12121.1; PID:d1012795; PID:g1435051
A;Note: the authors translated the codon ACG for residue 241 as His
C;Keywords: growth factor
F;78-368/Product: morphogen lefty #status predicted <MAT1>
F;136-368/Product: morphogen lefty #status predicted <MAT2>

  Query Match            84.2%;  Score 1531;  DB 2;  Length 368;
  Best Local Similarity  82.8%;  Pred. No. 1.4e-120;
  Matches  288;  Conservative   24;  Mismatches   34;  Indels    2;  Gaps    1;

Qy      3 ALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYVALLQRSHGDRSRGKRFSQ 62
          ||||||:|||||:|||| : | ||:||:| :|||:||| |||||||| ||  |||||||||
Db     21 ALTGEQILGSLLQQLQLDQPPVLDKADVEGMVIPSHVRTQYVALLQHSHASRSRGKRFSQ 80

Qy     63 SFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPKAALHRHGRLSPRS 122
          : ||||||||  | ||||||||||||||||||||||||||||||||: || |  |||| |
Db     81 NLREVAGRFLVSETSTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPRTALRRQKRLSPHS 140

Qy    123 ARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVNFWQQLSRPRQPLLLQ 182
          ||||||:|||| ||||||||:||||||||:||||||||||||||||||||||||||||||
Db    141 ARARVTIEWLRFRDDGSNRTALIDSRLVSIHESGWKAFDVTEAVNFWQQLSRPRQPLLLQ 200
```

```
Qy    183 VSVQREHLGPLASGAHKLVRFASQGAP--AGLGEPQLELHTLDLGDYGAQGDCDPEAPMT 240
          ||||||||||    :|||||||:|| |   | ||||||||||||| ||||||:||||||:|
Db    201 VSVQREHLGPGTWSSHKLVRFAAQGTPDGKGQGEPQLELHTLDLKDYGAQGNCDPEAPVT 260

Qy    241 EGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPPEALAFKWPFLGPRQCIA 300
          ||||||||||:||||||||||:|||||| ||||||| | ||:|  :||||||||||:|
Db    261 EGTRCCRQEMYLDLQGMKWAENWILEPPGFLTYECVGSCLQLPESLTSRWPFLGPRQCVA 320

Qy    301 SETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 348
          ||  |||||||:|||||||||||||||||| ||||||||||:||||||
Db    321 SEMTSLPMIVSVKEGGRTRPQVVSLPNMRVQTCSCASDGALIPRRLQP 368
```

Claims 39-51 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruben (N, PTO-892 2003-09-07).

Ruben discloses an isolated human lefty polypeptide having an amino acid sequence that is identical to SEQ ID NO: 114 of the present application, as indicated below:

```
AAY03850
ID   AAY03850 standard; Protein; 366 AA.
XX
AC   AAY03850;
XX
DT   18-JUN-1999  (first entry)
XX
DE   Human lefty protein.
XX
KW   Nodal protein; lefty protein; TGF-beta; sexual development; human;
KW   pituitary; cartilage; osteoarthritis; osteoporosis; haematopoiesis;
KW   periodontal disease; wound healing; tissue repair; tumour; cancer;
KW   interstitial lung disease; autoimmunity; leukaemia; lymphoma; immunity;
KW   immunosuppression; inflammatory bowel disease; myelosuppression;
KW   infectious disease; bone.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   Peptide         1..18
FT                   /note= "signal peptide"
FT   Protein         19..366
FT                   /note= "mature protein"
FT   Domain          78..364
FT                   /note= "first predicted TGF-beta like domain of lefty"
FT   Domain          136..366
FT                   /note= "second predicted TGF-beta like domain of lefty"
FT   Domain          143..366
FT                   /note= "third predicted TGF-beta like domain of lefty"
XX
PN   WO9909198-A1.
XX
PD   25-FEB-1999.
XX
PF   20-AUG-1998;   98WO-US17211.
XX
PR   21-AUG-1997;   97US-0056565.
XX
PA   (HUMA-) HUMAN GENOME SCI INC.
XX
PI   Ebner R,  Ruben SM,  Soppet DR;
XX
DR   WPI; 1999-190173/16.
DR   N-PSDB; AAX31925.
XX
PT   New isolate human Nodal and Lefty polypeptides
XX
PS   Claim 1; Fig 1B; 182pp; English.
```

```
XX
CC   The present invention relates to novel human nodal and lefty proteins
CC   which are members of the TGF-beta family. The human nodal and lefty
CC   proteins may be involved in a developmental process such as the correct
CC   formation of various structures or in one or more post-developmental
CC   capacities including sexual development, pituitary hormone production,
CC   and the creation of bone and cartilage. The Nodal and Lefty polypeptides
CC   are useful for enhancing or enriching the growth and/or differentiation
CC   of specific cell populations, eg. embryonic cells or stem cells. They can
CC   be used to treat such conditions as osteoarthritis, osteoporosis, and
CC   other abnormalities of bone, cartilate, muscle, tendon, ligament, and/or
CC   other connective tissues and/or organs such as liver, lung, cardiac,
CC   pancreas, and kidney. Compositions containing nodal and lefty proteins
CC   may be useful for growth formation, for treating periodontal disease and
CC   for modulating haematopoiesis, wound healing and tissue repair. They can
CC   also be used for the treatment of tumours, cancers, interstitial lung
CC   disease, and any disregulation of the growth and differentiation patterns
CC   of cell function including autoimmunity, arthritis, leukaemia, lymphomas,
CC   immunosuppression, immunity, humoral immunity, inflammatory bowel
CC   disease, myelosuppression, or infectious diseases. The present sequence
CC   represents a human lefty polypeptide. The cDNA encoding the lefty
CC   protein is deposited under the ATCC deposit No. 209091.
XX
SQ   Sequence   366 AA;

  Query Match             100.0%;  Score 1928;  DB 20;  Length 366;
  Best Local Similarity   100.0%;  Pred. No. 7.4e-183;
  Matches  366;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1 MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ 60

Qy      61 YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL 120

Qy     121 FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180

Qy     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240

Qy     241 DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP 300
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     241 DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP 300

Qy     301 PEALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     301 PEALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360

Qy     361 PRRLQP 366
           ||||||
Db     361 PRRLQP 366
```

Ruben also discloses recombinant expression of the polypeptide in eukaryotic host (paragraph bridging pages 64-65), which would result in cleavage of the signal peptide, and the recombinant expression of the polypeptide linked to an epitope tag (page 49, full paragraph 2) or to the Fc portion of an immunoglobulin (paragraph bridging pages 63-64).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kothapalli (W,2003-09-07 PTO-892 2003-09-07) in view of Meno (V,2003-09-07 PTO-892 2003-09-07).

Kothapalli discloses the deduced amino acid sequence of ebaf (Figure 5) having an amino acid sequence that is 95.6% identical to the amino acid sequence of SEQ ID NO: 114 and 95.9% identical to the amino acid sequence of amino acids 19-366 of SEQ ID NO: 114 of the present application, as indicated below:

```
TGF4_HUMAN
ID   TGF4_HUMAN     STANDARD;      PRT;   366 AA.
AC   O00292; O75611;
DT   01-NOV-1997 (Rel. 35, Created)
DT   16-OCT-2001 (Rel. 40, Last sequence update)
DT   15-JUN-2002 (Rel. 41, Last annotation update)
DE   Transforming growth factor beta 4 precursor (TGF-beta 4) (Endometrial
DE   bleeding-associated factor) (Left-right determination factor A)
DE   (Lefty-A protein).
GN   EBAF OR TGFB4 OR LEFTA OR LEFTYA.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Placenta;
RX   MEDLINE=97298127; PubMed=9153275;
RA   Kothapalli R., Buyuksal I., Wu S.-Q., Chegini N., Tabibzadeh S.;
RT   "Detection of ebaf, a novel human gene of the transforming growth
RT   factor beta superfamily association of gene expression with
RT   endometrial bleeding.";
RL   J. Clin. Invest. 99:2342-2350(1997).
RN   [2]
RP   REVISIONS.
RX   MEDLINE=99162193; PubMed=10053005;
RA   Kothapalli R.;
RL   Unpublished results, cited by:
RL   Kosaki K., Bassi M.T., Kosaki R., Lewin M., Belmont J., Schauer G.,
RL   Casey B.;
RL   Am. J. Hum. Genet. 64:712-721(1999).
RN   [3]
RP   SEQUENCE FROM N.A., AND VARIANT L-R AXIS MALFORMATIONS ASN-342.
RC   TISSUE=Placenta;
RX   MEDLINE=99162193; PubMed=10053005;
RA   Kosaki K., Bassi M.T., Kosaki R., Lewin M., Belmont J., Schauer G.,
```

```
RA   Casey B.;
RT   "Characterization and mutation analysis of human LEFTY A and LEFTY B,
RT   homologues of murine genes implicated in left-right axis
RT   development.";
RL   Am. J. Hum. Genet. 64:712-721(1999).
CC   -!- FUNCTION: REQUIRED FOR LEFT-RIGHT ASYMMETRY DETERMINATION OF
CC       ORGAN SYSTEMS IN MAMMALS. MAY PLAY A ROLE IN ENDOMETRIAL BLEEDING.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: MESENCHYMAL CELLS OF THE ENDOMETRIAL STROMA.
CC   -!- DEVELOPMENTAL STAGE: TRANSIENTLY EXPRESSED BEFORE AND DURING
CC       MENSTRUAL BLEEDING.
CC   -!- PTM: THE PROCESSING OF THE PROTEIN MAY ALSO OCCUR AT THE SECOND R-
CC       X-X-R SITE LOCATED AT AA 132-135. PROCESSING APPEARS TO BE
CC       REGULATED IN A CELL-TYPE SPECIFIC MANNER.
CC   -!- DISEASE: DEFECTS IN EBAF RESULT IN LEFT-RIGHT AXIS MALFORMATIONS
CC       INCLUDING LEFT PULMONARY ISOMERISM, CARDIAC ANOMALIES
CC       CHARACTERIZED BY COMPLETE ATRIOVENTRICULAR CANAL DEFECT AND
CC       HYPOPLASTIC LEFT VENTRICLE, AND INTERRUPTED INFERIOR VENA CAVA.
CC   -!- SIMILARITY: BELONGS TO THE TGF-BETA FAMILY.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U81523; AAB53269.1; ALT_SEQ.
DR   EMBL; AF081511; AAC32600.1; -.
DR   EMBL; AF081508; AAC32600.1; JOINED.
DR   EMBL; AF081509; AAC32600.1; JOINED.
DR   EMBL; AF081510; AAC32600.1; JOINED.
DR   EMBL; AF081513; AAD48145.1; -.
DR   HSSP; P10600; 1TGJ.
DR   Genew; HGNC:3122; EBAF.
DR   MIM; 601877; -.
DR   InterPro; IPR001839; TGFb.
DR   InterPro; IPR001111; TGFb_N.
DR   Pfam; PF00019; TGF-beta; 1.
DR   Pfam; PF00688; TGFb_propeptide; 1.
DR   ProDom; PD000357; TGFb; 1.
DR   SMART; SM00204; TGFB; 1.
DR   PROSITE; PS00250; TGF_BETA_1; 1.
KW   Developmental protein; Growth factor; Cytokine; Glycoprotein; Signal;
KW   Multigene family; Disease mutation.
FT   SIGNAL       1     21       POTENTIAL.
FT   PROPEP      22     76       OR 135 (POTENTIAL).
FT   CHAIN       77    366       TRANSFORMING GROWTH FACTOR BETA 4.
FT   DISULFID   251    264       BY SIMILARITY.
FT   DISULFID   263    316       BY SIMILARITY.
FT   DISULFID   293    351       BY SIMILARITY.
FT   DISULFID   297    353       BY SIMILARITY.
FT   CARBOHYD   158    158       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   VARIANT    342    342       S -> N (IN L-R AXIS MALFORMATIONS).
FT                               /PTId=VAR_010385.
SQ   SEQUENCE   366 AA;  40920 MW;  63A416CAE30F7A39 CRC64;

  Query Match             95.6%;  Score 1843;  DB 1;  Length 366;
  Best Local Similarity   95.6%;  Pred. No. 2.3e-144;
  Matches  350;  Conservative    5;  Mismatches   11;  Indels    0;  Gaps    0;

Qy       1 MQPLWLCWALWVLPLASPGAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQ 60
           | ||||||||||||||| |||||| |||||||||||||| ||| |||||||:|||| ||||||
Db       1 MWPLWLCWALWVLPLAGPGAALTEEQLLGSLLRQLQLSEVPVLDRADMEKLVIPAHVRAQ 60

Qy      61 YVALLQRSHGDRSRGKRFSQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRL 120
           || ||:|||||||||||||||||||||||| ||||||||||||||||||||||||||||||
Db      61 YVVLLRRSHGDRSRGKRFSQSFREVAGRFLASEASTHLLVFGMEQRLPPNSELVQAVLRL 120

Qy     121 FQEPVPKAALHRHGRLSPRSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180
           ||||||||||||||||||||:|||||||||||||||||||||||||||||||||||||||||
Db     121 FQEPVPKAALHRHGRLSPRSAQARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDV 180

Qy     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 TEAVNFWQQLSRPRQPLLLQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTL 240

Qy     241 DLGDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQP 300
```

```
            || ||||||||||||||||||||||||||||||||||:||||||||||||||||||:||
Db    241 DLRDYGAQGDCDPEAPMTEGTRCCRQEMYIDLQGMKWAKNWVLEPPGFLAYECVGTCQQP 300

Qy    301 PEALAFKWPFLGPRQCIASETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360
          |||||| |||||||||||||| ||||||||||||||||||||||||||||||||||||||||
Db    301 PEALAFNWPFLGPRQCIASETASLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALV 360

Qy    361 PRRLQP 366
          ||||||
Db    361 PRRLQP 366
```

```
TGF4_HUMAN
ID   TGF4_HUMAN     STANDARD;      PRT;   366 AA.
AC   O00292; O75611;
DT   01-NOV-1997 (Rel. 35, Created)
DT   16-OCT-2001 (Rel. 40, Last sequence update)
DT   15-JUN-2002 (Rel. 41, Last annotation update)
DE   Transforming growth factor beta 4 precursor (TGF-beta 4) (Endometrial
DE   bleeding-associated factor) (Left-right determination factor A)
DE   (Lefty-A protein).
GN   EBAF OR TGFB4 OR LEFTA OR LEFTYA.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Placenta;
RX   MEDLINE=97298127; PubMed=9153275;
RA   Kothapalli R., Buyuksal I., Wu S.-Q., Chegini N., Tabibzadeh S.;
RT   "Detection of ebaf, a novel human gene of the transforming growth
RT   factor beta superfamily association of gene expression with
RT   endometrial bleeding.";
RL   J. Clin. Invest. 99:2342-2350(1997).
RN   [2]
RP   REVISIONS.
RX   MEDLINE=99162193; PubMed=10053005;
RA   Kothapalli R.;
RL   Unpublished results, cited by:
RL   Kosaki K., Bassi M.T., Kosaki R., Lewin M., Belmont J., Schauer G.,
RL   Casey B.;
RL   Am. J. Hum. Genet. 64:712-721(1999).
RN   [3]
RP   SEQUENCE FROM N.A., AND VARIANT L-R AXIS MALFORMATIONS ASN-342.
RC   TISSUE=Placenta;
RX   MEDLINE=99162193; PubMed=10053005;
RA   Kosaki K., Bassi M.T., Kosaki R., Lewin M., Belmont J., Schauer G.,
RA   Casey B.;
RT   "Characterization and mutation analysis of human LEFTY A and LEFTY B,
RT   homologues of murine genes implicated in left-right axis
RT   development.";
RL   Am. J. Hum. Genet. 64:712-721(1999).
CC   -!- FUNCTION: REQUIRED FOR LEFT-RIGHT ASYMMETRY DETERMINATION OF
CC       ORGAN SYSTEMS IN MAMMALS. MAY PLAY A ROLE IN ENDOMETRIAL BLEEDING.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: MESENCHYMAL CELLS OF THE ENDOMETRIAL STROMA.
CC   -!- DEVELOPMENTAL STAGE: TRANSIENTLY EXPRESSED BEFORE AND DURING
CC       MENSTRUAL BLEEDING.
CC   -!- PTM: THE PROCESSING OF THE PROTEIN MAY ALSO OCCUR AT THE SECOND R-
CC       X-X-R SITE LOCATED AT AA 132-135. PROCESSING APPEARS TO BE
CC       REGULATED IN A CELL-TYPE SPECIFIC MANNER.
CC   -!- DISEASE: DEFECTS IN EBAF RESULT IN LEFT-RIGHT AXIS MALFORMATIONS
CC       INCLUDING LEFT PULMONARY ISOMERISM, CARDIAC ANOMALIES
CC       CHARACTERIZED BY COMPLETE ATRIOVENTRICULAR CANAL DEFECT AND
CC       HYPOPLASTIC LEFT VENTRICLE, AND INTERRUPTED INFERIOR VENA CAVA.
CC   -!- SIMILARITY: BELONGS TO THE TGF-BETA FAMILY.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
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CC   use by non-profit institutions as long as its content is in no way
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U81523; AAB53269.1; ALT_SEQ.
DR   EMBL; AF081511; AAC32600.1; -.
DR   EMBL; AF081508; AAC32600.1; JOINED.
```

```
DR   EMBL; AF081509; AAC32600.1; JOINED.
DR   EMBL; AF081510; AAC32600.1; JOINED.
DR   EMBL; AF081513; AAD48145.1; -.
DR   HSSP; P10600; 1TGJ.
DR   Genew; HGNC:3122; EBAF.
DR   MIM; 601877; -.
DR   InterPro; IPR001839; TGFb.
DR   InterPro; IPR001111; TGFb_N.
DR   Pfam; PF00019; TGF-beta; 1.
DR   Pfam; PF00688; TGFb_propeptide; 1.
DR   ProDom; PD000357; TGFb; 1.
DR   SMART; SM00204; TGFB; 1.
DR   PROSITE; PS00250; TGF_BETA_1; 1.
KW   Developmental protein; Growth factor; Cytokine; Glycoprotein; Signal;
KW   Multigene family; Disease mutation.
FT   SIGNAL        1     21       POTENTIAL.
FT   PROPEP       22     76       OR 135 (POTENTIAL).
FT   CHAIN        77    366       TRANSFORMING GROWTH FACTOR BETA 4.
FT   DISULFID    251    264       BY SIMILARITY.
FT   DISULFID    263    316       BY SIMILARITY.
FT   DISULFID    293    351       BY SIMILARITY.
FT   DISULFID    297    353       BY SIMILARITY.
FT   CARBOHYD    158    158       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   VARIANT     342    342       S -> N (IN L-R AXIS MALFORMATIONS).
FT                                /FTId=VAR_010385.
SQ   SEQUENCE   366 AA;  40920 MW;  63A416CAE30F7A39 CRC64;

  Query Match             95.9%;  Score 1745;  DB 1;  Length 366;
  Best Local Similarity   96.0%;  Pred. No. 1.8e-139;
  Matches  334;  Conservative    5;  Mismatches    9;  Indels    0;  Gaps    0;

Qy       1 GAALTGEQLLGSLLRQLQLKEVPTLDRADMEELVIPTHVRAQYVALLQRSHGDRSRGKRF 60
           ||||| ||||||||||||||| ||| |||||||:|||| ||||||| ||:||||||||||||
Db      19 GAALTEEQLLGSLLRQLQLSEVPVLDRADMEKLVIPAHVRAQYVVLLRRSHGDRSRGKRF 78

Qy      61 SQSFREVAGRFLALEASTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPKAALHRHGRLSP 120
           |||||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||
Db      79 SQSFREVAGRFLASEASTHLLVFGMEQRLPPNSELVQAVLRLFQEPVPKAALHRHGRLSP 138

Qy     121 RSARARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVNFWQQLSRPRQPLL 180
           |||:||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     139 RSAQARVTVEWLRVRDDGSNRTSLIDSRLVSVHESGWKAFDVTEAVNFWQQLSRPRQPLL 198

Qy     181 LQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTLDLGDYGAQGDCDPEAPMT 240
           ||||||||||||||||||||||||||||||||||||||||||||| ||||||||||||||||
Db     199 LQVSVQREHLGPLASGAHKLVRFASQGAPAGLGEPQLELHTLDLRDYGAQGDCDPEAPMT 258

Qy     241 EGTRCCRQEMYIDLQGMKWAENWVLEPPGFLAYECVGTCRQPPEALAFKWPFLGPRQCIA 300
           ||||||||||||||||||:|||||||||||||||:|||||||| ||||||||||||||||||
Db     259 EGTRCCRQEMYIDLQGMKWAKNWVLEPPGFLAYECVGTCQQPPEALAFNWPFLGPRQCIA 318

Qy     301 SETDSLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 348
           ||| ||||||||||||||||||||||||||||||||||||||||||||||
Db     319 SETASLPMIVSIKEGGRTRPQVVSLPNMRVQKCSCASDGALVPRRLQP 366
```

ebaf may be a component of the molecular repertoire that locally participates in normal menstrual as well as abnormal endometrial bleeding (page 2349, left column, full paragraph 2). Kothapalli does not teach an isolated ebaf polypeptide.

Meno teaches the recombinant expression of lefty (Figure 2). Meno does not teach an isolated ebaf polypeptide.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to recombinantly express and isolate ebaf, with a reasonable

expectation of success. One of ordinary skill in the art would be motivated to recombinantly express ebaf in order to study its participation in normal menstrual as well as abnormal endometrial bleeding. Both Kothapalli and Meno teach TGF-β superfamily members. It would have been prima facie obvious to recombinantly express a TGF-β superfamily member, such as ebaf, using the teachings of Meno regarding the recombinant expression of a TGF-β superfamily member. Expression of ebaf according to the teachings of Meno would result in a polypeptide lacking its associated signal peptide. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
2003-09-07